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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/520,946	08/30/95	BROW M	FORS-01756

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Cpy

Office Action Summary

Application No.	Applicant(s)
08/520,946	Brow, Lyamichev And Olive
Examiner	**Group Art Unit**
WILLIAM SANDALS	1636

☒ Responsive to communication(s) filed on *Jan 15, 1998* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits** is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 3-29, and 31-54* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3-29, and 31-54* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Drawings

1. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 3-29 and 31-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lyamichev et al. in view of Young, Seela and Roling, and Young et al.

The claims are drawn to a method for identifying strains of microorganisms, which may be bacteria, which may be selected from the group comprising members of the genera *Campylobacter, Escherichia, Mycobacterium, Salmonella, Shigella* and *Staphylococcus,* wherein the genus *mycobacterium* comprise strains of multi-drug resistant *Mycobacterium tuberculosis.* Also, the microorganism may be virus which may be selected from the group comprising hepatitis C virus (HCV) and simian immunodeficiency virus (SIV). The microorganisms are identified by cleaving the isolated nucleic acid of the microorganisms where the nucleic acid is treated to form

(secondary) cleavage structures. The cleavage structures are cleaved with a cleavage means. The cleavage means may be an enzyme, which may be a nuclease, which may be selected from the group consisting of "Cleavase BN", *Thermos aquaticus* DNA polymerase, *Thermus thermophilus* DNA polymerase, *Escherichia coli* E.O. III, and the *Saccharomyces cerevisiae* Rad1/Rad10 complex. The nucleic acid may comprise a nucleotide analog. The nucleotide analog may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The nucleic acid may be single stranded, or RNA or DNA or may be double stranded. The double stranded nucleic acid may be rendered single stranded. This may be done by exposing the double stranded nucleic acid to increased temperature. The cleavage products of the nucleic acid may be separated and then may be detected. The detected cleavage products may be compared with cleavage products of nucleic acid structures from reference microorganisms. The isolated nucleic acid may be a polymorphic locus which may be isolated by polymerase chain reaction (PCR). The PCR may be done with a nucleotide analog which may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The PCR primers may be matching or complementary to consensus gene sequences derived from the polymorphic locus, which may be ribosomal RNA, which may be 16S ribosomal RNA.

Lyamichev et al. (see entire reference) taught a method for cleaving an isolated nucleic acid where the nucleic acid was treated to form (secondary) cleavage structures. The cleavage structures were cleaved with a cleavage means. The cleavage means was an enzyme, which was a nuclease, which was selected from the group consisting of *Thermos aquatics* (Tac) DNA

polymerase and *Thermos thermophilous* (Tth) DNA polymerase. The nucleic acid may be single stranded, or RNA or DNA or may be double stranded. The double stranded nucleic acid may be rendered single stranded. This may be done by exposing the double stranded nucleic acid to increased temperature. The cleavage products of the nucleic acid may be separated and then may be detected. The detected cleavage products may be compared with cleavage products of reference nucleic acid structures. The isolated nucleic acid may be a polymorphic locus which may be isolated by polymerase chain reaction (PCR). The PCR primers may be matching or complementary to consensus gene sequences derived from the polymorphic locus. Lyamichev et. al. taught that this method can be used to optimize allele-specific PCR. The polymerase was also taught to be a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid.

Lyamichev et al. did not teach a method for identifying strains of microorganisms, which may be bacteria, which may be selected from the group comprising members of the genera *Campylobacter, Escherichia, Mycobacterium, Salmonella, Shigella* and *Staphylococcus,* wherein the genus *mycobacterium* comprise strains of multi-drug resistant *Mycobacterium tuberculosis.* Lyamichev et. al. also did not teach that the microorganism may be a virus which may be selected from the group comprising hepatitis C virus and simian immunodeficiency virus. The reference did not teach that the detected cleavage products may be compared with cleavage products of nucleic acid structures from reference microorganisms. Lyamichev et al. did not teach that the nucleic acid may comprise a nucleotide analog, where the nucleotide analog may be selected from

the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The reference did not teach that the PCR may be done with these nucleotide analogs or that the PCR primers were from ribosomal RNA, which may be 16S ribosomal RNA.

Young (see especially columns 3-4 and 10) taught the use of PCR with the nuclease *Thermos aquaticus* (Tac) DNA polymerase to identify the polymorphic loci of ribosomal 16S RNA from *Mycobacterium spp.* which increased the speed, accuracy and sensitivity of detection of disease causing microorganisms which were difficult to culture and could take up to several weeks to identify by culture methods.

Seela and Roling (see especially pages 55 and 61) taught the use of 7-deaza-dATP, 7-deaza-dGTP and dUTP in PCR reactions. The use of these nucleotide analogs helped protect the nucleic acids containing them from nuclease digestion, as well as reduce "read through" problems frequently encountered in polymerase reactions.

Young et al. (see especially the introduction) taught the use of PCR with the nuclease *Thermos thermophilous* DNA polymerase for the detection of hepatitis C virus (HCV) in clinical diagnostics, which was an effective means of direct detection of HCV that streamlined the procedure, reduced potential contamination of the reaction by eliminating the addition of a second enzyme and increased specificity of the primer extension.

It would have been obvious to combine the teachings of Lyamichev et al. with Young, Seela and Roling, and Young et al. to produce a method for identifying strains of microorganisms,

which may be bacteria or viruses, where the microorganisms were identified by cleaving the isolated nucleic acid which was treated to form (secondary) cleavage with a nuclease because Lyamichev et. al. taught that this method could be used to optimize allele-specific PCR. The polymerase was also taught to be a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid. Seela and Roling recited the use of Tac polymerase with nucleotide analogs 7-deaza-dATP, 7-deaza-dGTP and dUTP in PCR reactions and taught that the use of these nucleotide analogs would have helped protect the nucleic acids containing them from nuclease digestion, as well as reduce "read through" problems frequently encountered in polymerase reactions. Young et. al. taught the use of PCR with the nuclease *Thermos thermophilous* DNA polymerase for the detection of hepatitis C virus (HCV) in clinical diagnostics. They taught that the use of Tth DNA polymerase in PCR was an effective means of direct detection of HCV which streamlined the procedure and reduced potential contamination of the reaction by eliminating the addition of a second enzyme and increasing the specificity of the primer extension.

One of ordinary skill in the art would have been motivated to combine the teachings of Lyamichev et al. with Young, Seela and Roling, and Young et al. to produce a method that could be used to optimize allele-specific PCR wherein the polymerase is also a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid because Lyamichev et. al. taught that this method could be used to optimize allele-specific PCR. Lyamichev et al. also taught that the polymerase was a single stranded endonuclease which

recognized hairpin structures. Seela and Roling taught the method using Tth DNA polymerase or Tac DNA polymerase which incorporated nucleotide analogs 7-deaza-dATP, 7-deaza-dGTP and dUTP in PCR reactions demonstrating that the use of these nucleotide analogs helped protect the nucleic acids containing them from nuclease digestion, as well as reduce "read through" problems which are frequently encountered in polymerase reactions. Also, the use of nuclease *Thermos thermophilous* DNA polymerase in PCR assays was an effective means of direct detection of HCV as taught by Young et al. because it streamlined the procedure and reduced potential contamination of the reaction by eliminating the addition of a second enzyme which also increased the specificity of the primer extension. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Lyamichev et al., Young, Seela and Roling, and Young et al.

Conclusion

4. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the

examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
February 12, 1998

NANCY DEGEN
PRIMARY EXAMINER